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Long-term real-life adherence of percutaneous tibial nerve stimulation in over 400 patients

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Abstract

Background: Percutaneous tibial nerve stimulation (PTNS) is used as a treatment to reduce the complaints of overactive bladder (OAB). Although it is rewarding therapy patients need maintenance treatment to preserve the beneficial effect.

Aim: This real-life retrospective study was performed to assess the feasibility of PTNS adherence.

Materials & Methods: All patients who underwent PTNS were retrospectively included. We analyzed the following: indication, kind of treatments (pharmacologic and third-line therapy) before and after PTNS treatment, time and reason for quitting therapy. Statistical analysis was done by performing competitive-risk analysis and Kaplan-Meier curves. Patients were categorized into four groups. Group 1: all patients; group 2: all patients on maintenance PTNS therapy (continuing after 12 weeks); group 3: patients on maintenance PTNS therapy excluding the following: (a) patients with initial good response who seized treatment due to death, (b) patient who successfully switched to transcutaneous stimulation, (c) patients who were cured of their OAB symptoms, or (d) patients who relocated; and group 4: group 3 but excluding those who stopped treatment because of nonmedical reasons (physical strain, inconveniencies associated with visiting the hospital).

Results: Four-hundred two patients (70% female) with a median age of 70 years underwent PTNS. Underlying treatment indications were: OAB-wet (54%) and OAB-dry (29%). The median follow-up (FU) of group 1 was 4 months. Fifty-seven percent (N = 228) of the patients received maintenance PTNS therapy. Median FU in group 4 was 46 months (range, 3-111 months). Over 40% of the maintenance patients stopped PTNS because of logistic reasons and physical strain during an FU time of 6 years.

Conclusion: The real-world data described here with is in line with earlier published work in terms of the success rate of OAB treatment. However, over 40% quit their therapy due to nonmedical reasons.

KEYWORDS

neuromodulation, overactive bladder, PTNS, urge, urge-incontinence

1 | INTRODUCTION

In the treatment of overactive bladder (OAB), percutaneous tibial nerve stimulation (PTNS) is used to reduce complaints of patients. OAB is a feature of storage lower urinary tract symptoms (LUTS) characterized by urinary urgency with or without urinary incontinence (UI), usually with frequency and nocturia.[1] In Europe, the overall prevalence of OAB reported by women is 13% and 12% in men. Nearly half of the women who report symptoms of OAB also suffer from UI.[2] Behavioral therapy and pharmacologic therapy such as antimuscarinics or β-3 agonists are first lines of treatment in OAB. Although medication is the mainstay for OAB treatment, over 70% of all patients quit medication within 1 year because of intolerability or ineffectiveness.[3-5]

McGuire et al[6] were the first to report the use of transcutaneous tibial nerve stimulation for urologic conditions. Stoller modified the above therapy to a percutaneous technique by using a 34-gauge needle. This resulted in the reduction of complaints regarding urgency, frequency, urge incontinence, and pelvic pain.[7] The mechanism by which PTNS inhibits OAB complaints is not yet clearly defined. PTNS has clinical success rates ranging from 55% to 80%.[8-14] Although PTNS has gained its place in the treatment of OAB, real-life data on a substantial group of patients followed for a long time are scarce. Almost all published studies are clinical trials with a strict study-protocol. Real-life data presenting clinical rates of success or reasons for quitting this therapy is rare. If published, it is mainly a small number of patients or a short period of follow-up (FU). We hereby report the results during the long-term (median: 4 months, maximum: 111 months) FU of over 400 patients who underwent PTNS in our single-center (Rijnstate Hospital, Arnhem).

2 | MATERIALS AND METHODS

All patients who underwent PTNS (Urgent PC system) in our single-center hospital from January 2008 until July 2018 were retrospectively included. During the first 12 weeks patients were treated weekly with PTNS, while during maintenance treatment, PTNS was performed based on clinical symptoms indicated by the patient. PTNS technique applied was previously described by van Balken et al.[15] Baseline characteristics, indication for PTNS, time and/or reason for treatment discontinuation, and other treatments before and after PTNS were extracted from patients' files. Treatment success was determined based on subjective parameters. Together with the urologist, patients evaluated the beneficial effect after 12 weeks of treatment. Positive treatment outcomes warranted the continuation of maintenance therapy.

Patients were grouped into four categories based on response rate and reason for discontinuing treatment, to be able to analyze causes for treatment cessation. Group 1: all patients who ever had a PTNS treatment in our hospital (intention to treat population). Group 2: all patients during maintenance PTNS. These patients continued to maintenance therapy after 12 weeks of initial treatment and after concluding a positive therapy outcome with their urologist. Group 3: group 2 excluding those with a good response that did not continue due to relocation, death, switching to transcutaneous nerve stimulation or free of OAB complaints. Group 4: group 3 excluding patients who stopped treatment due to physical strain (painful ankle during maintenance PTNS) or practical problems to come to the hospital during the maintenance PTNS. Group 4 is, the purest group of successful PTNS treatment, to evaluate the long-term effect with correction for the initial good responders who stopped treatment due to reasons that are not related to treatment effect. This group represents the per protocol treated population.

We used SPSS 22.0 (SPSS, Chicago, IL) for statistical analysis. To evaluate the survival of the treatment Kaplan-Meier curves were used. Discontinuing PTNS was used as a survival event. We investigated the risk of quitting the therapy because of logistic reasons and physical strain by using competitive-risk analysis. Death and quitting the therapy was used as a competitive risk. The hospital's local ethical committee approved the study.

3 | RESULTS

From January 2008 until July 2018, 402 patients were included with a median age of 70 years, ranging from 19 to 80 (group 1). Seventy percent of the patients were female. The mean distance patients had to drive for their treatment was 13.8 km (ranging from 1.5 to 110 km). Indications for the treatment were: OAB-wet (54%), OAB-dry (29%), neurogenic bladder (defined as patients with multiple sclerosis, post-cerebrovascular accident (CVA), Parkinson's disease, dementia, myelopathy, spinal disc herniation, cerebellar ataxia, cauda equine syndrome, congenital diseases, and isolated neurogenic bladder; 15%), others (2%). Most patients had two different types of pharmacologic treatment previous to starting PTNS (range, 0-5). Some patients did not go through the initial OAB medication trial before PTNS due to patients' prior beliefs and/or preferences based on side effects or fear because of hypersensitivity/allergies. The median FU of group 1 (N = 402) was 4 months (ranging from

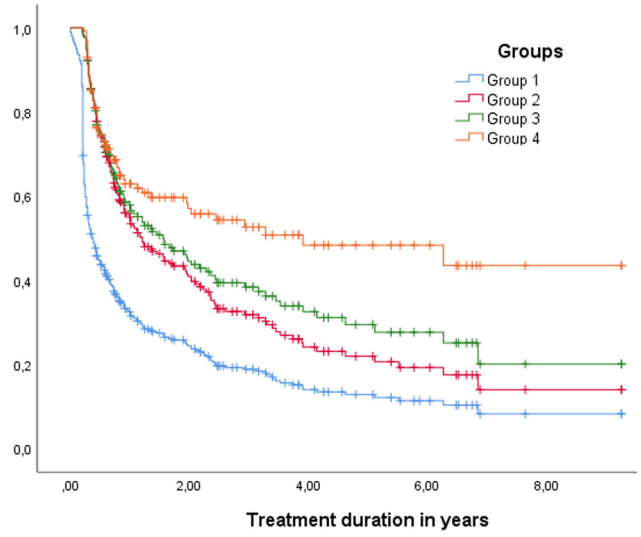

FIGURE 1 Treatment duration of percutaneous tibial nerve stimulation in months according to different groups

1-111 months). In group 2, 57% of the patients (N = 228) went into maintenance treatment after 12 weeks of initial PTNS treatment and after concluding on a positive outcome with their urologist with a median FU of 14 months (range, 3-111 months). Groups 3 (N = 183) and 4 (N = 131) had a median FU of 18 (range, 3-111 months) and 46 months (range, 3-111 months) (Figure 1).

Forty-five patients in group 2 stopped their treatment because of nonmedical reasons (two patients died, three patients relocated, 20 patients switched to transcutaneous electrical nerve stimulation (TENS) therapy, and 20 patients were free of complaints), leaving 183 patients in group 3. Switching to TENS therapy was mainly done due to the patient's preference. Only two patients were already treating themselves with TENS because of chronic pain whereby transcutaneous treatment for OAB was more convenient. In four patients the reason for switching to transcutaneous treatment was not reported.

In group 4 (N = 131), 57% of the patients still continue maintenance treatment nowadays. Fifty-two patients quitted their therapy because of physical strain (painful ankle) or logistic reasons (problems visiting the hospital). Figure 2 shows an estimation of the risk of quitting the therapy because of logistic reasons and physical strain. This is demonstrated that the risk of quitting therapy due to logistic reasons and physical strain, is over 40% at 6 years of FU for all patients during maintenance treatment.

Baseline criteria for the groups as described above are listed in Table 1. On the basis of the baseline criteria, we tried to provide a prediction model for this kind of patients. However, age, sex, number of therapies before PTNS, distance to the hospital, and etiology of OAB was not significant.

If patients did not continue their PTNS treatment, they mostly selected no treatment (57%) followed by botulinum toxin (14%), several different types of anticholinergics (13%), Mirabegron (10%), alternative medicine (4%), or pelvic floor treatment (2%).

4 | DISCUSSION

In this real-life data study, we report that 57% of our patients continues PTNS treatment after 12 weekly treatment sessions based on the decision made together with their urologist that the treatment was successful and the willingness to continue. This is in line with former studies that report success rates, defined as continuing treatment to maintenance therapy after 12 weeks of treatment, between 54.5% and 79.5%.[8-14,16]

Peters et al[17] described in the STEP study that over 75% of the study population with an initial good response after 12 weeks of treatment still benefit from the PTNS after 3 years of treatment. The average number of maintenance treatments in that study population was once a month.[17] In our analysis from daily practice, it can be shown that only 32% of all the patients who continued PTNS treatment after a good response to 12 weekly PTNS treatment (group 2), continues for a longer period with a maximum FU of 111 months. In this group, the median number of treatments during our FU period was 32 (range, 14-261). Various reasons can account for this discrepancy between our findings and the STEP study. One could be the inclusion criteria for the STEP study in which patients from the therapy arm of the SUmiT trial were allowed to participate if they reported bladder symptoms as moderately or markedly improved on the 7-point global response assessment.[17,18] If we compare

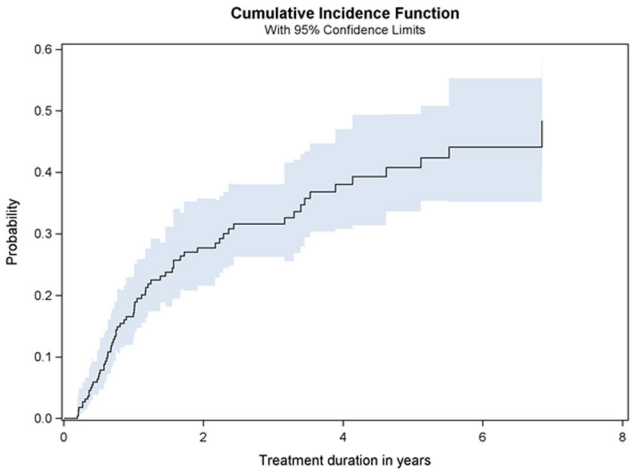

FIGURE 2 Risk analysis for quitting the treatment because of nonmedical reasons by using competitive risk-factor analysis

TABLE 1 Baseline criteria for the groups

	All/group 1	Group 2	Group 3	Group 4
Number of patients (n)	402	228	183	131
Men/women (n)	122/280	67/161	52/131	37/94
Median age, y	70 (19-80)	71 (23-76)	73 (23-76)	71 (26-76)
Median number of previous drug treatments	2 (0-5)	2 (0-4)	2 (0-4)	2 (0-4)
Median follow-up, mo	4	14	18	46
Maximum follow-up, mo	111	111	111	111

this to our group 4, 53% still continue their treatment after 3 years in a nonstudy population (Figure 1). The difference between the outcome in the STEP study and our results could be explained by the fact that our patients were not chosen based on specific eligibility criteria and the FU in a real-life cohort is not as strict as in a study-cohort. Recently Sirls et al[16] published their real-world experience in over 100 patients. They showed that 55% of the patients continued after 3 months of maintenance treatment which is more in line with our real-life data.

PTNS is a minimal invasive and cheap treatment modality without serious side effects compared with other surgical and drug therapies for OAB.[10,17] As described above, 57% of the patients continue after a good response for long-term treatment. In comparison to PTNS, OAB pharmacologic therapies have a higher rate of discontinuation within 1 year (mean 70%).[3-5] When comparing the long-term treatment outcomes of sacral nerve stimulation, van Kerrebroeck et al[19] showed 70% of the patients still experiencing a benefit after 5 years. In our real-life data, after 5 years 44% of patients in group 4 still benefited from the PTNS treatment. Nonetheless, due to the limited battery life of SNS systems, the average time for reoperations/explanations is 5 to 7 years.[19,20] In addition, although SNS therapy has demonstrated higher patient satisfaction at a 5-year time-point, the procedure is more complicated and has a higher level of serious adverse events. Therefore, PTNS can be considered an acceptable alternative for long-term treatment with good satisfaction levels and less serious complications as compared with SNS.

In our study, more than 40% of the subjects discontinued treatment after 6 years due to nonmedical reasons (Figure 2), indicating that although the therapy is beneficial still 40% eventually do not receive it due to practical reasons. We suspect that by minimizing the practical reasons for stopping treatment, more patients will continue for long-term treatment. This could be done by allowing patients to treat themselves at home by means of an implant. The first few pilot studies have recently been published with promising results.[21-23] The RENOVA iStim system (Bluewind Medical Ltd, Herzliya, Israel) showed a clinical success rate of 71% after 6 months based on a reduction in the number of leaks and/or voids and reduction in the number of episodes with a degree of urgency.[22] The eCOIN (Valencia Technologies Corp, Valencia, CA) showed similar success rates, 71% relative median reduction in the number of urgency urinary incontinence episodes after 12 weeks of treatment.[23] Long-term safety and efficacy outcomes are yet unknown. However, Janssen et al[24] published data at 9 years FU period after implantation of the first tibial nerve stimulation implant (Urgent SQ) for OAB indications. It was demonstrated that six of seven implanted patients still had sensory and locomotor responses on stimulation and all implants were still intact with no migration or displacement.[24,25] These results are promising for the treatment of OAB with a tibial implantable device.

This study is the first to present a large number of patients in a real-life setting. Physicians and patients should be aware of the fact that if the initial response to PTNS is good, the likelihood of maintaining this treatment benefit in the next few years is high. Patients tend to quit PTNS maintenance treatment due to multiple reasons, such as physical strain or inconveniencies associated with visiting the hospital. This information is relevant for patients and professionals in their decision making and also highly supports the need of development implantable tibial neurostimulation devices.

The fact that this study is a retrospective single-center study poses a limitation on reaching a solid conclusion. Therefore a prospective and possibly multi-institutional study is warranted.

5 | CONCLUSION

The real-world data we describe are in line with earlier published work in terms of the success rate of OAB treatment by PTNS. We demonstrated that PTNS is a successful long-term therapy modality. However, more than 40% of the patients quitted during maintenance treatment due to nonmedical reasons.

AUTHOR CONTRIBUTIONS

MD was involved in data collection and management, data analysis, and manuscript writing/editing; JH contributed in manuscript writing/editing; MVB also contributed in manuscript writing/editing and protocol/project development.

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